SYNOPSIS

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REFERENCE DIRECTING USERS TO APPROVED DRUG LABEL FOR PRESCRIBING INFORMATION

http://www.purduepharma.com/PI/prescription/Palladone.pdf

Proprietary Drug Name:	**Generic Drug Name:**	**Therapeutic area and FDA approved indications:**
Hydromorphone Hydrochloride Controlled-Release (HHCR)	Hydromorphone Hydrochloride	Analgesia

Name of Sponsor/Company: Purdue Pharma, L.P. | **Study Number**: HD95-0803

Title of the Study: Open-Label Study of the Effectiveness, Safety, and Pharmacokinetic and Pharmacodynamic Profiles of Oral Administration of Hydromorphone Hydrochloride Controlled-Release Capsules (QD) in Patients With Moderate to Severe Cancer-related Pain

Principal Study Investigators: Multiple investigators

Study Centre(s): 25 sites in the US.

Publication (Reference): None

Study Period: 08-Nov-1996 to 30-Nov-1998 | **Phase of Development:** Phase 3

Objectives: To evaluate the efficacy, safety, plasma concentration, and pharmacodynamic effect of oral administration of hydromorphone hydrochloride controlled-release (HHCR) capsules qd in the treatment of cancer-related pain.

Methodology: Multicenter, open-label, repeated-dose study that included only the test formulation (HHCR). Patients were enrolled following participation in 1 of 2 companion HHCR double-blind trials (HD95-0801 or HD95-0802). Subjects were diagnosed with cancer and required treatment of chronic cancer-related pain with opioid analgesics. Patients entered an 8-week core study period followed by optional extension periods.

Number of Patients (Planned and Analyzed): This was an optional, open-label continuation study in which all patients were enrolled from 1 of 2 double-blind HHCR pain studies, HD95-0801 or HD95-0802. A total of 144 patients enrolled; 143 received treatment and were included in the safety population, and 95 completed the 8-week core study period. Fifty-two patients enrolled, and 51 continued treatment after 8 weeks, in the extension period.

Diagnosis and Main Criteria for Inclusion/Exclusion: Male and female patients, aged at least 10 years, who required treatment of chronic cancer-related pain with opioid analgesics, and met the inclusion/ exclusion criteria specified in the protocol.

Test Product, Dose, and Mode of Administration, Batch Number:

Hydromorphone hydrochloride controlled-release capsules

Treatment	Maximum Dose	Dosage Form	Unit Strength	Lot Number(s)
HHCR qd	Determined by investigator	Capsule	12 mg	CB25-33 and 8K
HHCR qd	Determined by investigator	Capsule	16 mg	1L
HHCR qd	Determined by investigator	Capsule	24 mg	5L
HHCR qd	Determined by investigator	Capsule	32 mg	8L

Reference Therapy, Dose and Mode of Administration, Batch Number:

Hydromorphone hydrochloride immediate-release tablets

Treatment	Maximum Dose	Dosage Form	Unit Strength	Lot Number(s)
HHIR q4–6h prn	1/8 to 1/6 total daily dose of HHCR	Tablet	2 mg	CB25-38
Dilaudid® q4–6h prn	1/8 to 1/6 total daily dose of HHCR	Tablet	2 mg	11100227, (exp. Oct. 2002)
Dilaudid® q4–6h prn	1/8 to 1/6 total daily dose of HHCR	Tablet	4 mg	10900276, (exp. Aug. 2001) 10900187, (exp. May 2002) 10900206, (exp. July 2001)
Dilaudid® q4–6h prn	1/8 to 1/6 total daily dose of HHCR	Tablet	8 mg	11200116, (exp. May 2001) 11200047, (exp. April 2002) 11200096, (exp. April 2001)

Duration of Treatment: The maximum scheduled duration of treatment for the core study period was 8 weeks. Temporary leave from the study was permitted for up to 14 days; however, any days on temporary leave were included within the 8-week core study period. Following study completion, patients had the option to enter a 2-month extension period, followed by 1 or more additional 2-month extension periods. Each extension was to be approved by the sponsor prior to patients' continuation in the study.

Criteria for Evaluation:

Efficacy:

- Average weekly pain intensity ratings.
- Current pain intensity ratings on each of 2 PK/PD days.
- Daily dose of HHCR and rescue medication taken throughout the study. Number and timing of rescue medication doses.

Safety:

- Daily spontaneous reports of adverse events (reported by patient, caregiver, health provider, investigative staff).
- Pharmacodynamic ratings on each of 2 PK/PD days (weeks 2 and 6) of the core study period.

Pharmacokinetics:

- Actual and dose-adjusted plasma hydromorphone concentrations measured once at weeks 2 and 6 of the core study period.

Statistical Methods: Summary statistics are presented.

Results Summary:

Efficacy Results:

Primary Efficacy: The primary efficacy variables were weekly average pain intensity ratings and changes in average daily doses of HHCR and rescue (HHIR), both on a weekly and on a daily basis. There was little fluctuation in average pain intensity over the 8-week core study period (range across weeks, 2.8 to 3.1 on a 0–10 scale). The average daily dose of hydromorphone (HHCR + rescue combined) increased from 43.1 mg at week 1 to 55.7 mg at week 8. There was no change in HHCR dose for the majority (61.5%) of patients in the core study period. Overall, 15.7% of the total daily dose of hydromorphone hydrochloride (HHCR + rescue combined) was administered as rescue medication.

There was little fluctuation across days in the mean total daily dose (in total mg) of HHCR or rescue (HHIR) alone. The minimum fluctuations across days were less than 1 mg for both HHCR and HHIR rescue. The maximum fluctuations across days occurred in study week 8 (4.73 mg and 2.11 mg for HHCR and HHIR rescue, respectively).

Secondary Efficacy: Secondary efficacy variables for this study included the number and percentage of patients needing rescue, the timing of rescue doses, and patterns in HHCR dose titrations. The majority of patients (range, 79.4% to 86.6% across study weeks) took rescue medication at some point, and most took rescue doses 5 to 7 days a week. The percent of patients needing no rescue ranged from 14.0% to 22.2% across treatment weeks in the core study period.

The majority of rescue doses (approximately 80%) were taken during the first 16 hours of the day (starting at 8:00 AM), with a decrease during the nighttime hours (from midnight on) (nighttime use approximately 50% of daytime use, adjusting for the difference of 16 hours daytime vs 8 hours nighttime), suggesting continuous pain control at the end of the dosing period.

Most patients (61.5%) did not require a change in HHCR dose from the dose they were receiving at entry. Fifty-five patients (38.5%) had a change in HHCR dose (initial to final) during the core study period; 33.6% had an increase and 4.9% had a decrease. The most common reasons for upward titration were increased pain intensity and increased use of rescue medication. The most common reason for downward titration was an adverse event.

Safety Results:

- HHCR was well-tolerated by most patients, who were significantly ill with cancer. For the core study period, the majority of adverse events (irrespective of the investigator's opinion of relationship to study drug) were not serious (93.7%), were mild or moderate in severity (84.2%), and required no change in HHCR dose (95.9%).
- Adverse events occurring in $\geq$ 10% of patients during the 8-week core study period were somnolence, constipation, nausea, dizziness, vomiting, and pruritus (Table 2).
- Thirteen (9.0%) patients discontinued the study because of adverse events during the core study period, and 4 (7.7%) patients discontinued the study due to adverse events during the extension period. Eight of the 17 discontinuations were due to drug-related adverse events, and 4 of the 8 were due to well-described side effects of opioid analgesics (nausea, vomiting, dizziness, and sleepiness).
- Eight deaths occurred during the core study period, 8 during the extension period, and 3 within 7 days of completion or discontinuation from the study. No death was considered by the investigator to be related to study drug. Forty-eight patients were hospitalized during the core study period, and 25 patients were hospitalized during the extension period.

Pharmacokinetics: Observed mean dose-adjusted plasma hydromorphone concentrations were highest in patients assessed approximately 1 to 2 hours after dosing with HHCR. Plasma hydromorphone concentrations were relatively similar across patients assessed at various time points post-dosing with HHCR.

Conclusions:

- Eight weeks or more of HHCR treatment was well-tolerated in this patient population, who had significant underlying disease (cancer).
- In this setting, the safety profile of HHCR appeared to be similar to that established for HHIR.
- Long-term use of HHCR was associated with stable pain intensity scores and little need for change in the dose of HHCR or use of rescue medication.

Date of the Report: 17-Mar-2000

TABLE 2.
Study HD95-0803
Reports of Adverse Events Related[a] to study Medication reported by ≥ 10% of Patients (Core Study and Extension Period)

Adverse Event	Body System	Core Study HHCR (N = 143) n (%)	Extension Period HHCR (N = 52) n (%)
Somnolence	Nervous	68 (47.6)	14 (26.9)
Constipation	Digestive	67 (46.7)	21 (40.4)
Nausea	Digestive	47 (32.9)	9 (17.3)
Dizziness	Nervous	32 (22.4)	7 (13.5)
Vomiting	Digestive	27 (18.9)	7 (13.5)
Pruritus	Skin and appendages	21 (14.7)	0
Asthenia	Body	0	8 (15.4)

(Cross-references: Tables14.3.1.8.2.1 and 14.3.1.8.2.2)
[a]Considered by the investigator to be possibly, probably, or definitely related to study drug.